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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,784	09/15/2000	Malcolm L. Gefter	IMI-044DV3CN	3152

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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/662,784	GEFTER ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *95,96 and 101-104* is/are pending in the application.

4a) Of the above claim(s) *SEQ ID NO:8, 10 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *95,96 and 101-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *95,96 and 101-104* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-18-04 has been entered.

2. Applicant's arguments filed 6-18-04 have been entered into the record and have been fully considered. No amendments to the claims were newly presented in the 6-18-04. All claims are present as originally filed. Claims 95-96 and 101-104 are pending.

3. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the examiner.

Election/Restriction

4. Applicant's election with traverse of Group I, therapeutic compositions to the extent of SEQ ID NO:6, claims 95-96 and 101-104 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the groups do not differ from each other but are similar in structure function and search and would not place undue burden upon the Examiner. This is not found persuasive because the different SEQ ID Nos define differences in structural constraints in particular with respect to epitopes and therefore are capable of different effects and usage. Because the searches are different each from the other the searches are not co-extensive and a search for a single member would not reveal all pertinent art to

the other members. Further, it is noted that the search conducted for prior art pertinent to elected SEQ ID NO:6 reveals no similarity in hits to the alternative sequences of SEQ ID NO's 8, 10 and 16. Therefore, the search conducted for elected SEQ ID NO:6 further evidences that the searches are different, non-coextensive and fail to reveal pertinent prior art as to the alternative sequences of the claims.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

5. Claims 95-96 and 101-104 are objected to because of the following informalities: The claims are drawn in part to non-elected inventions as drawn to SEQ ID NO's:8, 10 and 16. Appropriate correction is required.

6. Claim 102 is objected to because of the following informalities: Claim 102 appears to require a comma between "antigen" and "to" to clarify the ratio required of the stimulation index within the claim, see in particular line 4.

Priority

7. Applicant's have noted support based upon PCT/US90/06548 (filed November 2, 1990) for the full length sequence of SEQ ID NO: 6, as noted at least in Figure 3.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 102 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. Claim 102 recites "at least approximately" with respect to the stimulation index and the positivity index. The term "at least approximately" is indefinite because the artisan can not perceived which of the terms is binding, i.e., whether the intended scope is of at least or approximately. If both or either is intended they should be separately recited as such.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 95-96 and 101-104 are rejected under 35 U.S.C. 102(a) as being anticipated by Littler et al., J. of Virol., 64(2):714-722, Feb. 1990 as evidenced by Harlow & Lane Cold Spring Harbor Labs, 1988, pp. 427.

Littler et al., teach identification, cloning and expression of the Major Capsid Protein gene of HHV-6. The MCP protein residues 354-360 share 100% identity with instant SEQ ID NO:6 residues 103-109 which define an epitope of at least 6 amino acids. The recombinantly produced peptides were electroeluted and inoculated three times i.p. with 10 ug of protein and then once i.v. with 2 ug protein. The proteins produced antibodies reactive with HHV-6 samples and the peptide was detected from serum antibodies from infected patients. The composition comprises a mixture as more than a single peptide is included in the

composition. As the peptides meet the structural limitations of the claims and the functional limitations of an eptiope, and the peptides are administered to animals producing an immunogen specific response, the reference teachings inherently anticipate a therapeutic composition comprising the peptide. The peptide compositions are the same and thus necessarily provide for those characteristics of a therapeutic composition as claimed. Similarly as the isolated peptides are the same as claimed, they necessarily provide for the properties of claim 102. The PTO has insufficient resources to determine whether or not the noted epitopes of Littler meet the limitations of claim 102. As noted in the specification, p. 48 the stimulation and positivity index is dependent upon the antigen as well as the patient and patient population of interest. Thus, the burden shifts to Applicants to show unobvious distinction. Claim 103 and 104 are directed to product-by process limitations which do not bear patentable weight as to the noted peptide segments. Nevertheless, the 103 rejection below is noted as directed to the product by process limitations. Thus, the reference teachings anticipate the claimed invention.

Applicants argue in the response of 2-3-03 that the peptides used for producing antibodies in Littler did not include a peptide consisting of residues 354-360 of MCP and thus fail to teach an epitope. Applicants further argue that epitopes involve at least 7 residues as in Linvingstone.

Applicants arguments filed 2-3-03 have been fully considered but are not persuasive. Applicants claims are not limited to "consisting of terminology" and the claims are directed to peptide compositions and peptides that are not

required to be administered. The Littler peptides are structurally and functionally the same as instant claims as evidenced via the definition of epitope as offered by either Harlow and Lane or Applicants Livingstone, and thus the properties of the same peptides as claimed are inherently provided. In particular Harlow & Lane teach contrary to Livingstone, i.e., that epitopes may be of only 4 or 5 amino acids, see in particular p. 427, lines 15-17. Nevertheless, residues 103-109 are of at least 7 residues. Thus the Littler peptides are consistent with the structural and functional limitations of the claims and thus inherently provide all characteristics absent factual evidence to the contrary. Moreover, the Examiner notes the breadth of the claims wherein the polypeptide may be at least a part of a sequence in common that has an epitope in common therewith and a modified form of a polypeptide that has at least one epitope in common therewith. As evidenced via the definition of epitope as in Harlow and Lane or Livingstone, the structural and functional limitations of an epitope are met.

Applicants argue in the response of 6-18-04 that Littler fails to teach the claimed structure. In particular, Applicants argue that MCP of HHV-6 is unrelated to TRFP with no known immunological cross-reactivity. Applicants note that Littler does not teach that the common portion contains at least one epitope, or an epitope in common with SEQ ID NO:6. In response, while this is true, the Examiner has set forth sound scientific reasoning that would indicate the peptide inherently comprises a common epitope as defined and recognized within the art, see in particular Harlow and Lane, of record, which teach that epitopes may be

defined by 4 or 5 amino acid residues in common, see in particular full paragraph with reference to linear or partial sequences.

Applicants argue that even if an epitope exists within this common stretch of amino acids, i.e., an epitope recognized within the context of the whole MCP protein, the epitope would not be recognized by a B or T cell specific for human T cell reactive protein (TRFP) as claimed. Applicants assert that a common epitope is one that is recognized on two different polypeptides by the same T or B cell receptor, i.e., in the present case, a T or B cell receptor specific for TRFP. Applicants assert that, "T and B-cell epitopes are involved in initiation and perpetuation of an immune response to a protein allergen. A T or B-cell epitope is the basic element, or smallest unit of recognition, by a T or B-cell receptor. Recognition of these epitopes leads to the production of a variety of cytokines, antibodies, and other immune modulators which, in turn, leads to the generation of allergic symptoms in individuals." In response, Applicants assert an alternative definition for "epitope" as used in the claim than the one evidenced by the Examiner. However, Applicants have provided no supportive documentation in favor of this asserted alternative definition. The Examiner fails to recognize this alternative definition as an art recognized term or as a definition provided via Applicants specification. Further, there is no further delineation of, "the smallest unit of recognition," as referred to therein. Further, the claims are not drawn to B- or T-cell receptor epitopes. The term "epitopes" is generically claimed and hence, even if an art recognized definition for T- or B-cell eptiopes exists that is different from that as defined via Harlow and Lane, the claim is not drawn to it,

i.e., specifically to B- or T-cell epitopes, and therefore the art of record as evidenced would still apply. No evidence is provided to support the argument that the shared structure does not comprise a shared epitope.

Applicants assert that, "A B cell specific for a cat protein allergen, i.e., TRFP, would not recognize a MCP since B-cell recognition of protein allergens depends on the recognition of complex conformational epitopes which are particular to the full-length (e.g., native) protein allergens. Therefore, a B cell which recognizes an epitope of a protein allergen, such as TRFP, would not recognize the same protein sequence within the context of another unrelated protein allergen which has an entirely different conformation, such as MCP." In response, Applicants arguments appear to assert that the only epitopes encompassed are conformational epitopes of TRFP. Conformational epitopes are those that are dependent upon secondary or tertiary folding of a particular protein. Such epitopes may be unrelated to the peptides linear sequences. Yet, here, the claims are not directed to conformational epitopes but "epitopes" in generic form and moreover are not directed to TRFP conformational epitopes. At most claim 95 refers to the limitation "wherein said composition can be used to reduce an allergic response to a cat antigen in an individual sensitive to said antigen. Yet this limitation is a use recitation bearing no patentable weight, structure or function to the composition. Claims 102 notes particular functional recitations of the composition. Yet the specification provides no guidance whereby the functional recitation is met. As the prior art is noted to provide for the structural limitations, the peptides are deemed to provide the functional

properties, absent convincing factual evidence to the contrary. While, the Examiner does not recognize Applicants alternative definition, Harlow and Lane address, at least in part, Applicants reference to conformational epitopes which may differ from linear epitopes. Nevertheless, Harlow and Lane teach the prevalence of epitopes based upon a peptides "primary structure" or amino acid sequence in denatured linear form. In particular Harlow and Lane note that, "there is a reasonable chance that a similar epitope can be found on another polypeptide. In some cases the common epitopes will form part of an important structural similarity between antigens, and monoclonal antibodies can be used to detect related antigens. Alternatively, the antibodies may detect small structural similarities confined only to the antibody combining site. This is particularly true for antibodies that recognize denaturation-resistant epitopes. Presumably this occurs because these antibodies recognize features found in the primary structure of the polypeptides." Thus, Harlow and Lane evidence in contrast to Applicants suggestion. The epitopes claimed encompass both conformational as well as linear epitiopes.

Applicant's argue that, "In other words, based on the fact that TRFP and MCP are structurally and functionally unrelated (e.g., have a different overall primary sequence and different glycosylation patterns), the seven amino acids of MCP which are shared with TRFP would not be recognized within the context of the native MCP by a B cell specific for TRFP, since these amino acids are in a very different structural context (e.g., secondary and tertiary conformation) within

the MCP as compared to the TRFP." In response, these arguments are essentially as above and are non-persuasive for the reasons noted above.

Applicants assert that, "It is well known that the reactivity of isolated peptides does not resemble the reactivity of the same region in the intact protein because of interactions with other parts of the molecule and the loss of flexibility." However, applicants have provide no evidence to support this determination. In contrast, as noted above via Harlow and Lane, the primary structural sequence of a peptide may be the basis for epitope recognition.

Applicants assert that, "Therefore, even assuming that the seven amino acid sequence within the primary structure of the MCP of human herpesvirus 6 does comprise a B or T cell epitope (which the Examiner has provided no evidence of), the amino acid sequence would not be recognized by a B or T cell specific for human T cell reactive protein. Indeed, it should be noted that the position of the seven amino acids shared between MCP and TRFP is vastly different within the MCP protein than it is within the TRFP allergen. Therefore, a B cell receptor specific for TRFP, which recognizes epitopes within the context of the full length TRFP in its native conformation, would not recognize the same linear sequences within an entirely different and unrelated protein, such as MCP. Similarly, a T cell specific for TRFP also would not recognize MCP since T cell recognition of protein allergens depends on the manner in which the whole protein is proteolytically processed and presented by antigen presenting cells (APCs) to T cell receptors. This process, and the nature of the peptides which are ultimately presented to T cells, differs for, every protein depending on its

structure, including the structure of critical regions outside the T cell epitopes. Therefore, peptides (such as those including the common seven amino acid sequence between TRFP and MCP) processed and presented by APCs from MCP, and their ability to be recognized by T cells, will significantly differ from those processed and presented by APCs from TRFP, based on the significant difference in overall structure between the two proteins." In response, these arguments are essentially as above but are not persuasive for the same reasons. Applicants fail to acknowledge the breadth of their claim. Harlow and Lane clearly evidence epitopes recognized via linear structure. While the Examiner acknowledges that conformational epitopes may be present, the claims are not so limited. A sound scientific basis for rejection has been set forth, namely that a linear epitope of 7 amino acids in common would be expected by the artisan, based upon the art recognized definition, to comprise an "epitope" as claimed. Rejection is maintained.

12. Claims 95-96 and 101-104 are rejected under 35 U.S.C. 102(a) as being anticipated by Littler et al., J. of Virol., 64(2):714-722, Feb. 1990 as evidenced by Harlow & Lane Cold Spring Harbor Labs, 1988, pp. 427 or in the alternative as obvious under 35 USC 103 in view of Littler et al., J. of Virol., 64(2):714-722, Feb. 1990 as evidenced by Harlow & Lane Cold Spring Harbor Labs, 1988, pp. 427.

Littler et al., teach identification, cloning and expression of the Major Capsid Protein gene of HHV-6. The MCP protein residues 354-360 share 100% identity with instant SEQ ID NO:6 residues 103-109 which define an epitope of at

least 6 amino acids. The recombinantly produced peptides were electroeluted and inoculated three times i.p. with 10 ug of protein and then once i.v. with 2 ug protein. The proteins produced antibodies reactive with HHV-6 samples and the peptide was detected from serum antibodies from infected patients. The composition comprises a mixture as more than a single peptide is included in the composition. As the peptides meet the structural limitations of the claims and the functional limitations of an eptiope, and the peptides are administered to animals producing an immunogen specific response, the reference teachings inherently anticipate a therapeutic composition comprising the peptide. The peptide compositions are the same and thus necessarily provide for those characteristics of a therapeutic composition as claimed. Similarly as the isolated peptides are the same as claimed, they necessarily provide for the properties of claim 102 absent evidence to the contrary. The PTO has insufficient resources to determine whether or not the noted epitopes of Littler meet the limitations of claim 102, a polypeptide with stimulation index of at least approximately 4 or a positivity index of at lease approximately 250. As noted in the specification, pp. 46-48 the stimulation and positivity index are dependent upon the antigen as well as the patient and patient population of interest. Thus, the burden shifts to Applicants to show unobvious distinction. The Examiner is unable to determine whether or not exposure of the Littler peptide and or epitopes are sufficient to provide for the requisite stimulation and positivity indexes when tested amongst individuals. However, as noted above the peptides are noted to meet the structural and functional limitations of an epitope and thus inherently provide the

limitations of parent claim 101. The USPTO has insufficient resources and facts to determine whether the respective indexes are "inherently the same" or "obvious" because the Examiner cannot determine whether the exposure of the peptides is sufficient to meet the limitations. The Examiner is not in a position to determine inherency or obviousness because the record does not establish how the steps are the same or differ. Since the record does not allow such determination, the burden shifts to Applicants to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

Claim 103 and 104 are directed to product-by process limitations which do not bear patentable weight as to the noted peptide segments. Nevertheless, the 103 rejection below is noted as directed to the product by process limitations. Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claim 104 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Littler et al., J. of Virol., 64(2):714-722 in view of Hirschmann et al., US Patent No. 3,846,399 Nov. 5, 1974 as evidenced by Harlow & Lane Cold Spring Harbor Labs, 1988, pp. 427, lines 15-17.

Littler et al., teach as set forth above.

However, Littler et al., do not teach synthesis of the isolated polypeptide of claim 101 produced via chemical synthesis.

Hirschmann et al., teach a process for controlled stepwise chemical synthesis of peptides, see in particular Abstract, claims 1-9. The process provides the advantage of producing chemically pure polypeptides without the need for further purification, see in particular col. 2, lines 20-30, col. 8, lines 64-68.

Thus, it would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to use the process of chemical synthesis as taught by Hirschmann to produce the peptides of cat allergen. One of skill in the art would have expected success given the high skill in the art of chemically synthesizing amino acid peptides, the similarity of peptides produced recombinantly and chemically and the ability to stimulate antibodies with such

peptides without the requirement of further purification from cell culture. The purity would ensure proper antigenicity as recognized by the reference teachings. Thus, the cumulative reference teachings render the invention obvious to one skilled in the art.

Applicants argue as set forth above that the Littler reference does not teach the invention.

Applicant's arguments have been fully considered but are not persuasive. Contrary to Livingstone, Harlow & Lane teach epitopes of only 4-5 amino acids and therefore the reference teachings render obvious the broadest reasonable interpretation of the claims.

Status of Claims

15. No claims are allowed.

CONCLUSION

16. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

Sharon L. Turner, Ph.D.
September 3, 2004

SHARON L. TURNER, PH.D.
PATENT EXAMINER
9-3-04